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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PATENT, COPYRIGHT & TRADEMARK LAW GROUP
4199 Kinross Lakes Parkway
Suite 275
RICHFIELD, OH 44286

EXAMINER
BRADLEY, CHRISTINA

ART UNIT	PAPER NUMBER
1654	

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09/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,861	GENKIN ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Must be DETAILED ACTION

Status of Claims

1. Claims 1-4 and 6-14 are pending.

Priority

2. Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on an application filed in Russia on 7/14/2003. A new oath that acknowledges the filing of any foreign application was filed on 6/24/2008.

Specification

3. The objection to the abstract of the disclosure is withdrawn in light of the amendment filed 06/24/2008

Claim Objections

4. The previously issued objections to claims 1-14 are withdrawn in light of the amendment filed 06/24/2008.

5. Claims 1-14 are objected to because of the following grammatical errors: in claim 1, the use of the phrase “method for of treatment”; in claim 3, the two spaces after the comma following "activity"; in claim 3, line 4, “then” should be “than”; and claim 8 is missing a verb after "DNAse I (Dormase alpha)”. Appropriate correction is required.

Claim Rejections - 35 USC § 112/101

6. The rejection of claims 1-14 under 35 U.S.C. 101 and 112, second paragraph, is withdrawn in light of the amendment filed 06/24/2008.

Claim Rejections - 35 USC § 112, second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. The rejections regarding the limitations "introducing of blood extracellular DNA destroying agent" and "the treatment" in claim 1, "which characterized by" in claim 2, "wherein bovine pancreatic DNAse is used" in claim 6, "wherein human recombinant DNAse is used" in claim 7, "wherein in addition to the said treatment an agent binding extracellular DNA is introduced" in claim 10, "polymery" in claim 12, "said agent" in claim 13, "said agent" in claim 14, and "systemic blood circulation" in claims 1-14 are withdrawn in light of the amendment filed 06/24/2008.

9. The following new grounds of rejection are made.

10. Claims 1-4 and 6-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 1 recites the limitation "said treatment agent destroys extracellular DNA said blood of said cancer patient". The relationship between the extracellular DNA and blood in this limitation is undefined.

12. Claim 1 recites the limitation "certain oncological diseases". The specification does not define the term "certain" in a manner that clearly establishes the metes and bounds of the genus oncological diseases.

13. Claim 1 recites the limitation a method for treatment of lung carcinoma, breast cancer, gastric and colon cancer, kidney cancer…" It is not clear from this construction whether gastric cancer and colon cancer are separate alternatives of disease to be treated by the method or

whether gastric and colon cancer is one type of specific condition in which the patient is suffering from cancer of both locations.

14. Claim 1 recites a method of treating several types of cancers and oncological diseases by introducing a treatment agent into a circulating blood system of a cancer patient. The claim language does not clearly link the patient population to which the treatment agent is administered to the conditions intended to be treated by the method.

15. Claim 1 recites the limitation "blood extracellular DNA destroying agent". The term "destroying agent" is not defined in the specification. The specification also fails to define destroyed DNA. Several interpretations exist including hydrolysis of DNA to smaller fragments, hydrolysis of DNA to nucleotides, and a breakdown of the molecule to carbon, nitrogen, hydrogen, oxygen and phosphorous. In addition, the agent could act indirectly on the DNA, reducing its presence in blood by inhibiting its production.

16. Claim 4 recites the limitation "wherein said treatment is carried out during no less than 48 hours uninterruptedly." This limitation is not clearly defined in the specification. Uninterrupted could be interpreted to mean continuous administration or infusion, or administration of discrete doses over the course of 48 hours.

17. Claim 9 recites the limitation "wherein the treatment is carried out for a term of life" This limitation is not defined in the specification. The term of life could refer to a full-term of life, a remaining term of life or a subset of a term of life. The limitation does not specify whose term of life is being referred to.

Claim Rejections - 35 USC § 112, first paragraph

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1-4 and 6-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Erlich carcinoma in mice, lung carcinoma in humans and malignant and low differentiated lymphoma metastasized in the liver of humans by administering DNAse to patients, and for treating Erlich carcinoma in mice by administering DNAse and anti-DNA antibodies, does not reasonably provide enablement for treating all other oncological diseases with DNAse with or without the addition of "modificating agents" or other DNA binding agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and are as follows:

The Nature of the Invention

20. The invention is drawn to a method for treating oncological diseases by administering DNAse as a blood extracellular DNA destroying agent.

The State of the Prior Art and its Predictability or Unpredictability

21. Anker *et al.* (*Leukemia*, **2001**, *15*, 289-91 teach that circulating DNA levels are higher in the blood of cancer patients than in healthy controls (page 289). The prior art does not teach or suggest that cancer can be treated by reducing the circulating DNA levels.

22. The prior art of Young (WO 2001074905) and Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70) teaches that ovarian cancer can be treated by intravenous injection of the

DNaseI/huHMFG-1 Fab fusion protein and that DNAse I reduces tumor metastasis, respectively, but does not teach that the mechanism of action of the DNAse I is the destruction of extracellular DNA in the blood stream of the cancer patients. There is no guidance in the prior art on how to use DNAse to destror extracellular DNA to effectively treat cancer.

23. The cancer treatment and biopharmaceutical art is highly unpredictable, as underscored Ulrich & Friend (*Nature*, **2002**, *1*, 84-88), Ashton (*Nature Biotech*, **2001**, *19*, 307-311), and Gibbs *et al.* (*Science*, **2000**, *287*, 1969-1973) who discuss the difficulties in drug development and the high failure rates of candidate drugs in clinical trials.

The Relative Skill of Those in the Art

24. It is not within the ordinary skill of the art to treat cancer by destroying extracellular DNA in the circulating blood stream of cancer patients.

The breadth of the claims

25. The claims are exceptionally broad with respect to the diseases to be treated. Oncological diseases include all types of cancer known to affect humans and animals.

The Amount of Direction or Guidance Presented and the Presence of Working Examples

26. The specification presents working examples of the treatment of three oncological diseases: Erlich carcinoma in mice (examples 1 and 2), lung carcinoma in humans (example 3) and malignant, low differentiated lymphoma metastasized in the liver of humans (example 4). In each case, the administration of DNAse resulted in a reduction in circulating extracellular DNA and tumor. The specification fails to provide working examples for the treatment of any additional oncological diseases.

27. The specification presents only one working example of an "agent binding the blood extracellular DNA", polyclonal serum containing anti-DNA antibodies (example 6). The specification fails to define agent binding the blood extracellular DNA", and to provide guidance on how to isolate other agents with the claimed ability to bind extracellular DNA.

28. The specification fails to present a single working example involving the administration of a "modificating agent". Example 7 describes the effect of "modificating agents" on the pathogenic properties of DNA that has been extracted from plasma, and then subsequently administered to patients, but does not describe the effect of directly administering the "modificating agent".

The Quantity of Experimentation Necessary

29. The extent of guidance and working examples presented in the specification is insufficient to enable the full scope of the claimed methods. One cannot extrapolate the teachings of the specification, which are limited to three narrow conditions, to the full scope of the claims, which are broadly drawn to methods for treating all malignant tumors and oncological diseases by targeting extracellular DNA with DNAse. There is no evidence in the prior art or the specification to suggest that the destruction of extracellular DNA in the blood of cancer patients is a universally effective means to combat the disease. As a result the skilled artisan would be burdened with testing DNAse in a large number of models for different oncological diseases. Furthermore, the skilled artisan would be burdened with testing and developing compounds representative of the full scope of binding agents in claim 10. The experimentation required represents years of inventive effort. When the above factors are

weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

30. Claims 1-4 and 6-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

31. Originally filed claim 1 was drawn to a method of treating oncological diseases by introducing a blood extracellular DNA destroying agent. In the response filed 06/24/2008, claim 1 was amended to a method of treating lung carcinoma, breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma, malignant lymphoma and certain oncological diseases. Thus, the scope of the diseases to be treated by the method of claim 1 has been narrowed from all oncological diseases to lung carcinoma, breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma, malignant lymphoma and certain oncological diseases. The specification as originally filed fails to support this amendment. This is a new matter rejection.

32. The claim terms lung carcinoma, breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma, malignant lymphoma and certain oncological diseases do not appear in the specification as originally filed and are therefore not explicitly supported in the specification. Although one of ordinary skill in the art would recognize that lung carcinoma, breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma,

malignant lymphoma and certain oncological diseases are species in the genus of oncological diseases, one of ordinary skill in the art would not select these specific diseases for treatment with DNAse from amongst the entire genus. There is no suggestion or guidance in either the specification or prior art that would lead to this sub-genus. Therefore, the amendment is not implicitly supported in the specification as originally filed.

Claim Rejections - 35 USC § 102

33. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

34. The rejection of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Ngan *et al.* (*Ann. NY Acad. Sci.*, **2001**, *945*, 73-79) is withdrawn in light of the amendment filed 06/24/2008.

35. Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Young (WO 2001074905). Young teaches the use of the DNase-I/huHMFG-1 Fab fusion protein in the treatment of ovarian cancer. Patients diagnosed with ovarian cancer are treated by intravenous injection of the DNaseI/huHMFG-1 Fab fusion protein.

36. Claims 1, 3 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70). Sugihara *et al.* teach a method comprising administering DNAse I to subjects with malignant tumors by intravenous injection (p. 67, col. 1, para. 2). Sugihara *et al.* do not explicitly teach that extracellular DNA circulating in the blood of the cancer patient is destroyed. Because the active steps of the prior art method are identical to the

claimed method, that is the administration of the identical agent, DNAse I, to an identical patient population, mice with malignant tumors, the prior art inherently meets this additional functional limitation. With respect to claim 10, the DNAse I is administered in phosphate buffered saline. Cations and water molecules present in the solution constitute agents that are capable of binding to DNA.

Claim Rejections - 35 USC § 103

37. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

38. Claims 1-4, 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young (WO 2001074905). Young teaches the use of the DNase-I/huHMFG-1 Fab fusion protein in the treatment of ovarian cancer. Patients diagnosed with ovarian cancer are treated by intravenous injection of the DNaseI/huHMFG-1 Fab fusion protein (p. 40, lns. 24-26). Young does not teach the specific dosage regiments recited in claims 2, 4, 6 and 9. MPEP § 2144.05 states: "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. [W]here the general conditions of a claim are disclosed

in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In the instant case, given the teaching in the prior art that DNAse I can be used to treat ovarian cancer, it would have been obvious to optimize dosage and treatment schedule through routine optimization.

39. Claims 1-4, 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70). Sugihara *et al.* teach a method comprising administering DNAse I to subjects with malignant tumors wherein extracellular DNA circulating in the blood would necessarily be destroyed. Sugihara *et al.* do not teach the specific dosage regiments recited in claims 2, 4, 6 and 9. MPEP § 2144.05 states: "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In the instant case, given the teaching in the prior art that DNAse I can be used to prevent metastases, it would have been obvious to optimize dosage and treatment schedule through routine optimization.

40. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70) and Young (WO 2001074905), as applied to claims 1-4, 6 and 9 above, in further view of Shak *et al.* (*Proc. Natl. Acad. Sci.*, **1990**, *87*, 9188-9192). Neither Sugihara *et al.* or Young teach the use of human recombinant DNAse. Shak *et l.* teach the cloning, expression and characterization of human recombinant DNAse I. It would have been obvious to substitute the human recombinant DNAse I taught by Shak *et al.* in the methods of administering bovine DNAse I taught by Sugihara *et al.* and Young. The skilled artisan would

have been motivated to do so based on the teaching of Shak *et al.* that the use of the human enzyme could reduce side effects observed with the use of the bovine enzyme (p. 9188, col. 2). There would have been a reasonable expectation of success given that the enzymes posses the same structure and activity (p. 9189-91). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

41. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70) and Young (WO 2001074905), as applied to claims 1-4, 6 and 9 above, in further view of Leland *et al.* (*Chem. & Bio.*, **2001**, *8*, 405-13). Neither Sugihara *et al.* or Young teach the use of ribonuclease to treat oncological disease. Leland *et al.* teach that onconase, a ribonuclease, is in clinical trials as a cancer chemotherapeutic (abstract). MPEP § 2144.06 states: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." Therefore, it would have been obvious to combine the DNAse of Sugihara *et al.* and Young with the RNAse of Leland *et al.* given that both agents have anticancer effects.

42. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara *et al.* (*Br. J. Cancer*, **1993**, *67*, 66-70), Young (WO 2001074905) and Leland *et al.* (*Chem. & Bio.*, **2001**, *8*, 405-13), as applied to claims 1-4, 6 and 9 above, in further view of Nestle & Roberts (*J. Biol. Chem.*, **1969**, *244*, 5213-5218). Neither Sugihara *et al.*, Young or Leland *et al.* teach the use of ribonuclease from *Serratia marcescens*. Nestle & Roberts teach the ribonuclease from *Serratia marcescens*. It would have been obvious to use the ribonuclease from *Serratia*

marcescens given that it possesses the enxymatic activity responsible for the therapeutic effects of the ribonclease taught by Leland *et al.*

Double Patenting

43. The rejection of claims 1-3 and 5 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10/564,609 is withdrawn in light of the terminal disclaimer filed 06/24/2008.

44. The rejection of claims 1-3 and 5 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 13 of copending Application No. 10/546,615 is withdrawn in light of the terminal disclaimer filed 06/24/2008.

Conclusion

45. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654